

Impact of Donor Type in Patients with AML Given Allogeneic Hematopoietic Cell Transplantation After Low-Dose TBI-Based Regimen



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Abstract

Background: We assessed the impact of donor type in acute myeloid leukemia (AML) patients transplanted with 2 Gy total body irradiation (TBI)-based nonmyeloablative conditioning regimen.

Experimental Design: Data from 1,715 adult patients, with AML in CR1 or CR2 were included in this retrospective survey.

Results: Donors consisted either of HLA-matched sibling donors (MSD, $n = 701$), 10/10 HLA-matched unrelated donors (MUD, $n = 611$), HLA-haploidentical donors (haplo, $n = 112$) or single or double umbilical cord bloods (CBT, $n = 291$). Chronic graft-versus-host disease (GVHD) was less frequent in CBT (28%) and in haplo (30%) patients than in MSD (50%) and MUD (51%) recipients ($P < 0.001$). Two-year incidence of relapse was 32%, 30%, 34%, and 34% in MSD, MUD, CBT and haplo patients,

respectively ($P = 0.7$). Two-year overall (OS) and GVHD-free relapse-free survival (GRFS) were 59% and 29% in MSD patients, 56% and 39% in CBT recipients, 53% and 23% in MUD recipients, and 43% and 37% in haplo patients, respectively. In multivariate analyses, MUD patients had lower GRFS than MSD patients beyond day 100 (HR 1.3, $P = 0.001$) while CBT was associated with a better GRFS than MSD beyond day 100 (HR 0.6, $P = 0.002$).

Conclusions: In this large cohort of AML patients transplanted following low-dose TBI-based conditioning, the relapse incidence was not affected by donor type suggesting that the intensity of GvL effects might be comparable with these four transplant approaches. Furthermore, CBT was associated with better GRFS beyond day 100 than MSD while the opposite was observed for MUD. *Clin Cancer Res*; 1–10. ©2018 AACR.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is increasingly used in older patients with acute myeloid leukemia (AML; refs. 1–3). On the basis of discoveries in a preclinical canine model of transplantation (4), a truly nonmyeloablative conditioning regimen consisting of 2 Gy total body irradiation (TBI) with or without added fludarabine has been developed by the Seattle team (5–8). This conditioning allowed successful engraftment with minimal toxicities with either HLA-identical sibling or HLA-matched unrelated donors (5, 8–14). Identical backbone has later been adapted by adding pretransplant or pre- and posttransplant cyclophosphamide (Cy) to allow successful umbilical cord blood (CBT) or HLA-haploidentical (haplo) transplantation, respectively (15–19).

Low-dose TBI-based nonmyeloablative allo-HCT relies nearly exclusively on immune-mediated graft-versus-leukemia (GvL) effects for tumor eradication (20–23). As GvL effects are in a large part directed against genetic disparities between the patient and his donor, one could speculate that increasing genetic disparities between the donor and the recipient might result in higher GvL effects (24, 25). Here, we assessed the impact of donor type on transplantation outcomes in a large cohort of AML patients transplanted in CR with low-dose TBI-based nonmyeloablative conditioning regimens.

Translational Relevance

Relapse incidence was not affected by donor type suggesting that the intensity of GVL effects is comparable with these four transplant approaches. Further, LFS was comparable with these four transplant approaches. Finally, GRFS beyond day 100 was better with MSD than with MUD while GRFS beyond day 100 was better with CBT than with MSD.

Patients and Methods

Data collection

This is a retrospective, multicenter registry-based study performed by the Acute Leukemia Working Party (ALWP) of the European society for Blood and Marrow Transplantation (EBMT). EBMT registry is a voluntary working group of more than 500 transplant centers, participants of which are required once a year to report all consecutive stem cell transplantations and follow-up. Audits are routinely performed to determine the accuracy of the data. Inclusion criteria were adult (≥ 18 years) patients, *de novo* or secondary AML in first (CR1) or second (CR2) complete remission, transplantation between 2004 and 2016, conditioning with fludarabine + 2 Gy TBI with or without pre- or posttransplant cyclophosphamide, no *in vitro* or *in vivo* (other than posttransplant Cy, i.e., no ATG and no alemtuzumab) T-cell depletion of the graft, and either an HLA-matched sibling donor (MSD), a 10/10 HLA-matched unrelated donor (MUD), an HLA-haplo-identical donor (Haplo), or a single or double umbilical cord blood (CBT). For CBT, HLA-compatibility requirements followed the current practice of antigen level typing for HLA-A and -B and allele-level typing of HLA-DRB1. CB units were 4–6/6 HLA-A, -B, and -DRB1 matched to the recipient in all patients and to the other unit in case of double CBT in most patients (26, 27). HLA disparities between each unit and the recipient and between the two units were not necessarily at the same loci. The choice between single or double CBT was done according to transplant center policy (26, 28). Generally, double CBT was performed when a single unit with adequate cell dose was not available. Grading of acute and chronic GVHD was performed using established criteria (29).

For the purpose of this study, all necessary data were collected according to EBMT guidelines.

Ethics approval and consent to participate

The scientific board of the ALWP of EBMT approved this study.

Statistical analyses

Data from all patients meeting the inclusion/exclusion criteria were included in the analyses. We did not censor patients who did not engraft. Furthermore, as the comparison of donor type was done in an intent-to-treat principle, we did not censor patients at time of second allo-HCT. The latter was given in 52 MSD, 27 MUD, 5 haplo, and 20 CBT patients, respectively. Patient, disease, and transplant-related characteristics for the 4 cohorts (MSD/UD/CBT/Haplo) were compared by using χ^2 statistics for categorical variables and the Kruskal–Wallis test for continuous variables. Start time was date of transplant for all endpoints. As follow-up duration varied

significantly between the 4 groups, all survival times were censored 2 years after transplantation. Measured outcomes were leukemia-free survival (LFS), relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS), acute graft-versus-host disease (aGVHD), chronic graft-versus-host-disease (cGVHD), and GVHD and relapse-free survival (GRFS). LFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the presence of 5% bone marrow blasts and/or reappearance of the underlying disease. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from alloSCT to death, regardless of the cause. GRFS was defined as being alive with neither grade III–IV acute GVHD, extensive chronic GVHD nor disease relapse (30). Neutrophil engraftment was defined as first of 3 consecutive days with a neutrophil count of at least $0.5 \times 10^9/L$.

Cumulative incidences were used to estimate the endpoints of NRM, RI, engraftment, and acute and chronic GVHD to accommodate for competing risks. To study acute and chronic GVHD, we considered relapse and death to be competing events. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. Univariate analyses were done using the Gray test for cumulative incidence functions and the log rank test for OS, GRFS, and LFS.

Associations between donor type (MSD, MUD, haplo, CBT) and transplantation outcomes were evaluated in multivariable analyses, using Cox proportional hazards. All variables differing significantly between the 4 groups or factors known to influence outcomes were included in the Cox model. Variables introduced in the Cox models included recipient age (in decades), year of transplantation, disease status at allo-HCT, primary or secondary AML, cytogenetic risk, female donor to male recipient or not, and patient and donor CMV serostatus. To test for a centre effect, we introduced a random effect or frailty for each center into the model (31). Proportional hazards assumptions were checked systematically for all proposed models using the Grambsch–Therneau residual-based test. Proportionality assumption was significantly violated when studying GRFS, relapse, and nonrelapse mortality. We thus split the follow-up of these endpoints at day 100. This cut-off point was chosen based on a clinical rationale, after occurrence of acute GVHD and before occurrence of chronic GVHD.

All tests were two sided. The type I error rate was fixed at 0.017 for determination of factors associated with time to event outcomes after using the Bonferroni correction for three comparisons. Statistical analyses were performed with SPSS 24.0 (SPSS Inc) and R 3.4.1 (<https://www.R-project.org/>).

Results

Patients and donors

Data from all 1,715 patients meeting the inclusion/exclusion criteria were included in the analyses. They received grafts from either MSD ($n = 701$), MUD ($n = 611$), or haplo ($n = 112$) donors or were given single or double CBT ($n = 291$; Table 1). The proportion of patients transplanted in CR1 was 86%, 80%, 66%, and 61% in MSD, MUD, haplo, and CBT groups, respectively ($P < 0.001$). Median patient age at transplantation was 58, 62, 58, and 55 years, respectively (global $P < 0.001$). The proportion of patients with secondary AML was 15%, 20%, 14%, and 18% in MSD, MUD, haplo, and CBT groups (global

Table 1. Patient and transplant characteristics

| | MSD (n = 701) | UD 10/10 (n = 611) | Haplo (n = 112) | CBT (n = 291) | UD10/10 vs. MSD ^a | Haplo vs. MSD ^a | CBT vs. MSD ^a |
|--|------------------|-----------------------|------------------------|------------------|---------------------------------|-------------------------------|-----------------------------|
| Median patient age, y (range) | 58 (18–74) | 62 (18–77) | 58 (19–74) | 55 (18–73) | <0.001 | 0.6 | <0.001 |
| Median follow-up, mo (range) | 66 (1–155) | 30 (1–132) | 18 (2–95) | 49 (3–152) | <0.001 | <0.001 | 0.001 |
| Median year of Tx | 2010 | 2012 | 2014 | 2010 | <0.001 | <0.001 | 0.1 |
| Median time from diagnosis to Tx in CR1 patients, mo (IQR) | 4.2 (3.4–5.2) | 4.7 (3.7–5.9) | 5.3 (4.4–7.0) | 5.8 (5.1–7.2) | <0.001 | <0.001 | <0.001 |
| Median time from diagnosis to Tx in CR2 patients, mo (IQR) | 18 (13–26) | 21 (15–28) | 20 (13–27) | 21 (15–27) | 0.3 | 0.5 | 0.13 |
| Recipient gender M, # (%) | 375 (54) | 328 (54) | 67 (60) | 133 (46) | 0.9 | 0.2 | 0.03 |
| F donor to M recipient, # (%) | 188 (27) | 53 (9) | 20 (18) | 60 (21) | <0.001 | 0.05 | 0.08 |
| Median donor age, y (range) | 55 (15–79) | 30 (18–58) | 34 (18–70) | NA | <0.001 | <0.001 | NA |
| Karnofsky performance status at Tx | | | | | 0.5 | 0.8 | 0.9 |
| <80 | 43 (7) | 34 (6) | 8 (8) | 17 (7) | | | |
| ≥80 | 587 (93) | 542 (94) | 97 (92) | 240 (93) | | | |
| Missing | 71 | 35 | 7 | 34 | | | |
| Diagnosis, # (%) | | | | | 0.009 | 0.9 | 0.3 |
| De novo AML | 597 (85) | 487 (80) | 96 (86) | 240 (82) | | | |
| Secondary AML | 104 (15) | 124 (20) | 16 (14) | 51 (18) | | | |
| Status at Tx, # (%) | | | | | 0.002 | <0.001 | <0.001 |
| CR1 | 606 (86) | 490 (80) | 74 (66) | 177 (61) | | | |
| CR2 | 95 (14) | 121 (20) | 38 (34) | 114 (39) | | | |
| Stem cell source | | | | | 0.2 | <0.001 | NA |
| Bone marrow | 15 (2) | 11 (2) | 53 (47) | NA | | | |
| Peripheral blood stem cells | 685 (98) | 600 (98) | 59 (53) | NA | | | |
| Single CBT | NA | NA | NA | 82 (28) | | | |
| Double CBT | NA | NA | NA | 209 (72) | | | |
| Cytogenetics, # (%) | | | | | 0.4 | 0.5 | 0.5 |
| Good risk ^b | 38 (8) | 18 (6) | 7 (9) | 19 (9) | | | |
| Intermediate risk ^c | 333 (71) | 204 (69) | 53 (65) | 146 (66) | | | |
| High risk ^d | 100 (21) | 73 (25) | 22 (27) | 55 (25) | | | |
| Not reported/failed | 230 | 316 | 30 | 71 | | | |
| FLT3-ITD, # (%) | | | | | 0.009 | 0.03 | 0.4 |
| Negative | 129 (68) | 99 (63) | 44 (83) | 64 (63) | | | |
| Positive | 61 (32) | 59 (37) | 9 (17) | 38 (37) | | | |
| Missing | 511 | 453 | 59 | 189 | | | |
| Patient CMV seropositive, # (%) | 472 (68) | 387 (64) | 78 (70) | 180 (63) | 0.2 | 0.7 | 0.1 |
| Fludarabine dose (mg/m ²), # (%) | | | | | NS | <0.001 | <0.001 |
| 90 | 548 (89) | 516 (91) | 0 | 1 | | | |
| 150 | 65 (11) | 49 (9) | 94 (100) | 23 (9) | | | |
| 200 | 3 (0.5) | 2 (0.5) | 0 | 221 (90) | | | |
| Missing | 85 | 44 | 18 | 46 | | | |
| Postgrafting immunosuppression, # (%) | | | | | | | |
| CSP (or tacro) + MMF | 627 (90) | 547 (90) | 0 | 268 (92) | <0.001 | <0.001 | <0.001 |
| Posttransplant cyclophosphamide ^e | 33 (4) | 34 (6) | 112 (100) ^f | 3 (1) | | | |
| Other | 41 (6) | 30 (5) | 0 | 20 (8) | | | |

Abbreviations: #, number of patients; CBT, cord blood transplantation; CR, complete remission; CSP, cyclosporine; diagn, diagnosis; FLT3-ITD, FMS-related tyrosine kinase 3 internal tandem duplication; IQR, interquartile ranges; M, male; MSD, HLA-matched sibling donor; MMF, mycophenolate mofetil; Tx, transplantation; UD, unrelated donor; Y, year.

^aCalculated with χ^2 statistics for categorical variables and Mann-Whitney test for continuous variables.

^bDefined as t(8;21), t(15;17), inv or del (16), or acute promyelocytic leukemia, these abnormalities only or combined with others.

^cDefined as all cytogenetics not belonging to the good or high risk (including trisomias).

^dDefined as 11q23 abnormalities, complex karyotype, abnormalities of chromosomes 5 and 7. No patient received ATG or alemtuzumab.

^eWith or without added immunosuppressive drugs.

^f105 patients received CSP (or tacro) + MMF, 4 patients CSP, 1 patient MMF and 2 patients other immunosuppressive drugs in addition to post-transplant cyclophosphamide.

$P = 0.06$). Median follow-up was 66, 30, 18, and 49 months, respectively (global $P < 0.001$). Stem cell source was peripheral blood stem cells (PBSC) in 98% of MSD and MUD recipients, but 53% in haplo patients. Post grafting immunosuppression consisted mainly on a combination of calcineurin inhibitors + MMF in MSD, MUD and CBT patients, while all haplo patients received in addition posttransplant Cy for rejection/GVHD prophylaxis. As mentioned in the Patients and Methods section of the article, the use of ATG or alemtuzumab was an exclusion criterion in this survey.

Engraftment and GVHD

Graft rejection occurred in 2% of each MSD and MUD recipients, 5% of haplo patients, and 6% of CBT recipients ($P < 0.001$). Cumulative incidences of neutrophil engraftment were 98%, 98%, 95%, and 94%, respectively (global $P < 0.001$). At day 30, the figures were 94%, 95%, 90%, and 80%, respectively (global $P < 0.001$). Second allo-HCT as treatment of graft failure was offered in 5 of 16 MSD patients, 9 of 12 MUD patients, 1 of 6 haplo patients, and 5 of 20 CBT recipients. Two-year OS in the 54 patients with graft failure was 37%.

Grade II–IV acute graft-versus-host disease (GVHD) was more frequent in CBT (38%), haplo (31%), and MUD (30%) recipients than in MSD recipients (19%; global $P < 0.001$; Fig. 1A). Grade III–IV acute GVHD was more frequent in CBT (15%) than in MUD (9%), haplo (7%), or MSD (7%) recipients (global $P < 0.001$). In multivariate analysis, in comparison with MSD, CBT, and MUD were associated with a higher incidence of grade II–IV acute GVHD while grade III–IV acute GVHD was more frequent in CBT than in MSD recipients (Table 2).

Chronic GVHD was less frequent in CBT (28%) and in haplo (30%) patients than in MSD (50%) and MUD (51%) recipients ($P < 0.001$; Fig. 1A). Similarly, extensive chronic GVHD was less frequent in CBT (9%) and in haplo (11%) patients than in MSD (31%) and MUD (34%) recipients ($P < 0.001$). In multivariate analysis, in comparison with MSD recipients those given CBT had a lower incidence of chronic and extensive chronic GVHD while MUD had a higher incidence of chronic and extensive chronic GVHD (Table 2). Female donor to male recipients was also associated with a higher incidence of chronic (HR=1.4; 95% CI, 1.1–1.7; $P = 0.008$) and extensive chronic (HR=1.6; 95% CI, 1.2–2.2; $P = 0.003$) GVHD.

Relapse and NRM

Two-year incidence of relapse was 32% in MSD patients, 30% in MUD recipients, and 34% in CBT and haplo recipients, respectively ($P = 0.7$; Fig. 1B). In multivariate analyses, there was no impact of donor type on the risk of relapse. Factors associated with higher risk of relapse included intermediate (HR=1.5; 95% CI, 1.0–2.1; $P = 0.04$) or adverse cytogenetics (HR=3.4; 95% CI, 2.3–5.1; $P < 0.001$) and donor CMV seropositivity (HR=1.3; 95% CI, 1.1–1.5; $P = 0.009$), while female donor to male recipient (HR=0.7; 95% CI, 0.6–0.9; $P = 0.015$) was associated with a lower risk of relapse (Table 3).

Two-year incidence of nonrelapse mortality (NRM) was 13% in MSD patients, 20% in MUD recipients, 16% in CBT recipients, and 22% in haplo patients, respectively ($P < 0.001$; Fig. 1A). In multivariate analyses, in comparison with MSD patients, each other donor type was associated with a significantly higher NRM the first 100 days after transplantation while MUD recipients had also higher NRM beyond day 100. Furthermore, increasing age at transplantation (per 10 year; HR=1.4; 95% CI, 1.2–1.6; $P < 0.001$) and female donor to male recipients (HR=1.7; 95% CI, 1.3–2.3; $P < 0.001$) were also associated with higher NRM (Table 3).

LFS and OS

Two-year LFS was 54% in MSD patients, 50% in MUD and in CBT recipients, and 44% in haplo patients (global $P = 0.14$; Fig. 1B). Factors associated with worse LFS in multivariate analysis included intermediate (HR=1.6; 95% CI, 1.0–2.4; $P = 0.04$) and adverse (HR=2.9; 95% CI, 1.8–4.5; $P < 0.001$) cytogenetics, while a similar trend was observed for secondary AML (HR=1.3; 95% CI, 1.0–1.7; $P = 0.06$; Table 4).

Two-year OS was 59% in MSD patients, 56% in CBT recipients ($P = 0.5$ in comparison with MSD), 53% in MUD recipients ($P = 0.004$ in comparison with MSD), and 43% in haplo patients ($P = 0.02$ in comparison with MSD; Fig. 1B). In multivariate analysis there was a suggestion of lower OS in haplo ($P = 0.09$) than in MSD recipients (Table 4). Factors associated with worse OS in multivariate analysis included intermediate (HR=1.9; 95% CI, 1.2–3.1; $P = 0.01$) and adverse (HR=3.4; 95% CI, 2.0–5.7;

$P < 0.001$) risk cytogenetics, and secondary AML (HR=1.4; 95% CI, 1.0–1.8; $P = 0.04$).

AML relapse, GVHD, and infections were the primary causes of death during the whole study period for 27%, 7%, and 5% of MSD recipients, 21%, 8%, and 7% of MUD recipients, 18%, 5%, and 12% of haplo recipients, and 28%, 8%, and 5% of CBT recipients, respectively (Supplementary Table S1).

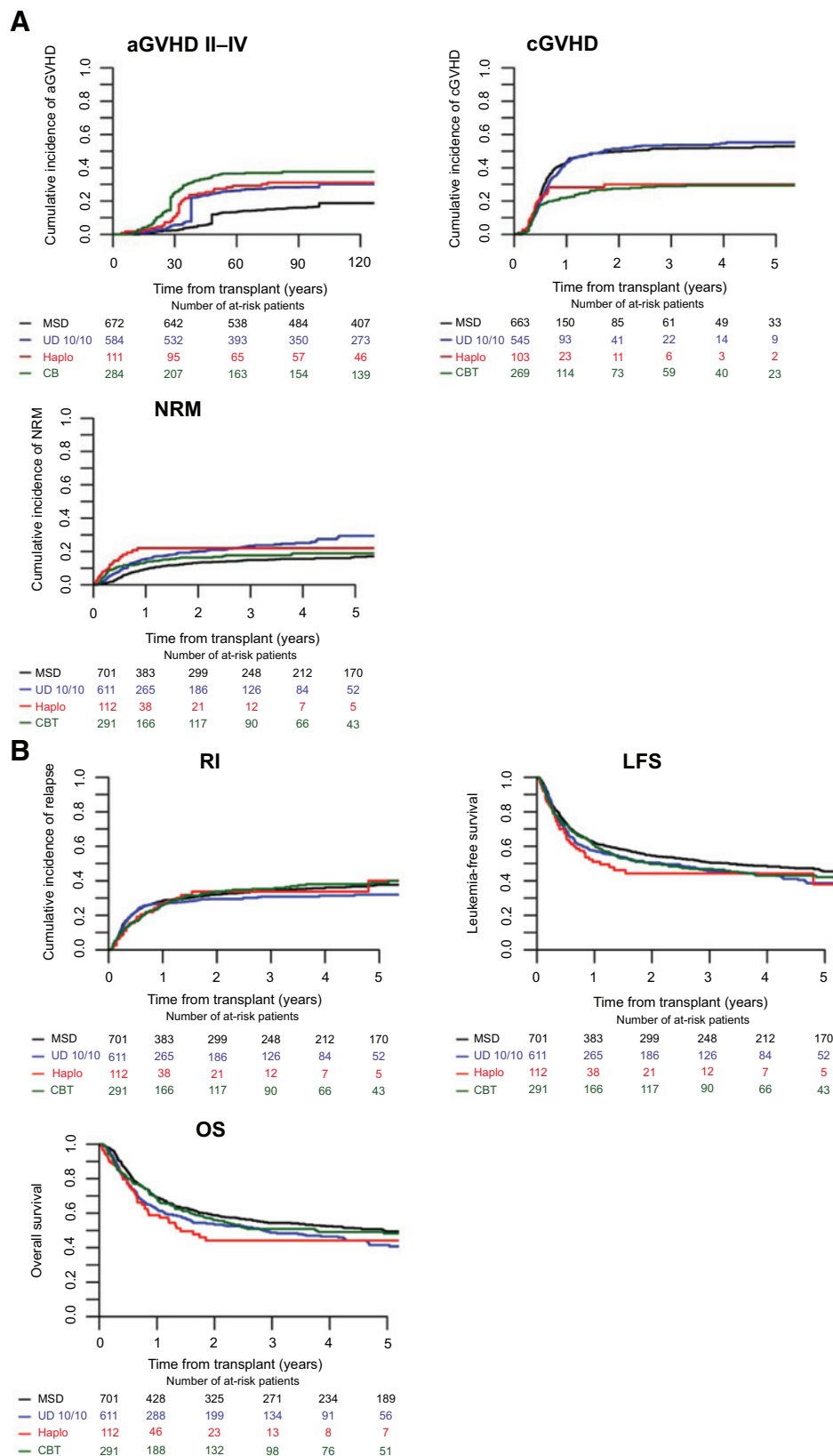
GRFS

GVHD and relapse-free survival (GRFS) is increasingly recognized as a major endpoint in allo-HCT (30, 32, 33). Two-year GRFS was 39% in CBT recipients, 37% in haplo patients, 29% in MSD patients, and 23% only in MUD recipients ($P = 0.0002$; Fig. 2). Since proportionality assumption was significantly violated when studying GRFS (due to a higher incidence of grade III–IV acute but a lower incidence of severe chronic GVHD in CBT recipients), we split the follow-up at day 100 (before and after the potential occurrence of classical acute GVHD). In comparison with MSD, CBT before day 100 was associated with worse GRFS. However, after day 100, CBT was associated with a significantly better GRFS. In contrast, MUD was associated with a significantly worse GRFS (Table 3). Other factors associated with worse GRFS in multivariate analyses included intermediate (HR = 1.4; 95% CI, 1.0–1.9; $P = 0.03$) and adverse (HR = 2.1; 95% CI, 1.5–2.9; $P < 0.001$) risk cytogenetics, and female donor to male recipient (HR = 1.2; 95% CI, 1.0–1.5; $P = 0.03$). In contrast, more recent transplantation was associated with better GRFS (HR = 0.98; 95% CI, 0.95–0.99; $P = 0.047$).

Discussion

Recent progress in haplo-HCT has changed the algorithm of donor selection in many transplantation centers (34, 35). Consequently, haplo-HCT is increasingly used in Europe while the use of CBT is declining (36). Several recent studies assessing the impact of donor type on transplantation outcomes have been reported (19, 24, 37–44). Limitation of these studies include the use of conditioning regimens of various intensities, inclusion of patients with various diagnoses, and/or relatively low number of patients (19, 24, 37–44). Here, we assessed the impact of donor type on transplantation outcomes in a large cohort of AML patients transplanted with a low-dose TBI-based nonmyeloablative regimen. Several observations were made.

A first observation was that the relapse incidence was comparable between MSD, MUD, haplo, and CBT patients. As nonmyeloablative allo-HCT relies nearly exclusively on GvL effects for tumor eradication, our data suggest that the magnitude of GvL effects is comparable with these different approaches, although some caution should be given for the haplo group given the relatively low number of patients in that group and their relatively short follow-up. Also one cannot exclude that the higher doses of fludarabine (and additional Cy) given to secure engraftment in CBT and haplo patients might have provided a little additional antileukemic effects. Previous studies using various conditioning regimens also observed a comparable risk of relapse between MSD and MUD (20, 22, 43, 45), MSD and haplo (24, 39, 42), MUD and haplo (43, 44), MUD and CBT (37), and between CBT and haplo (38). In contrast, another study observed a higher risk of relapse in haplo than in MUD in the setting of reduced-intensity conditioning (40). It is possible that posttransplant Cy administered in all haplo patients impacted GvL effects. Unfortunately, the number of MSD/MUD patients given

**Figure 1.**

A, Acute (a) GVHD, chronic (c) GVHD and NRM according to donor type. **B**, Relapse incidence, LFS, and OS according to donor type.

Table 2. Multivariate analyses for GVHD

| | Acute GVHD II-IV | | Acute GVHD III-IV | | Chronic GVHD | | Extensive chronic GVHD | |
|----------------------------|------------------|--------|-------------------|-------|---------------|--------|------------------------|--------|
| | HR (CI) | P | HR (CI) | P | HR (CI) | P | HR (CI) | P |
| MSD (reference) | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| MUD 10/10 | 1.9 (1.4-2.7) | <0.001 | 0.9 (0.5-1.8) | 0.76 | 1.3 (1.0-1.7) | 0.04 | 1.6 (1.2-2.3) | 0.005 |
| Haplo | 1.5 (0.9-2.7) | 0.14 | 1.1 (0.4-2.9) | 0.92 | 0.7 (0.4-1.2) | 0.19 | 0.5 (0.2-1.3) | 0.14 |
| CBT | 2.9 (2.0-4.4) | <0.001 | 2.9 (1.5-5.6) | 0.001 | 0.4 (0.3-0.6) | <0.001 | 0.3 (0.2-0.5) | <0.001 |
| CR2 vs. CR1 | 0.8 (0.5-1.1) | 0.10 | 0.6 (0.3-1.1) | 0.08 | 1.1 (0.8-1.4) | 0.57 | 1.1 (0.7-1.6) | 0.69 |
| Age (per 10y) | 1.1 (1.0-1.2) | 0.14 | 1.1 (0.9-1.4) | 0.33 | 1.0 (0.9-1.1) | 0.94 | 1.0 (0.8-1.1) | 0.63 |
| Year of Tx | 1.0 (1.0-1.0) | 0.91 | 1.0 (0.9-1.1) | 0.88 | 1.0 (0.9-1.0) | 0.09 | 0.9 (0.9-1.0) | 0.003 |
| Good risk (reference) | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Intermediate risk | 1.4 (0.8-2.4) | 0.30 | 1.2 (0.5-3.1) | 0.72 | 1.0 (0.7-1.4) | 0.79 | 1.2 (0.7-2.0) | 0.56 |
| Adverse risk | 1.5 (0.8-2.8) | 0.23 | 0.8 (0.3-2.5) | 0.75 | 0.9 (0.6-1.5) | 0.77 | 1.3 (0.7-2.4) | 0.42 |
| Sec. AML | 0.7 (0.5-1.1) | 0.14 | 1.0 (0.5-2.0) | 0.91 | 0.8 (0.6-1.2) | 0.26 | 0.8 (0.5-1.3) | 0.42 |
| Female D to male vs. other | 1.3 (0.9-1.7) | 0.17 | 1.1 (0.6-1.9) | 0.78 | 1.4 (1.1-1.7) | 0.01 | 1.6 (1.2-2.2) | 0.003 |
| Patient CMV positive | 0.8 (0.6-1.1) | 0.22 | 1.1 (0.7-1.8) | 0.68 | 1.0 (0.8-1.3) | 0.78 | 1.1 (0.8-1.5) | 0.38 |
| Donor CMV positive | 1.1 (0.9-1.5) | 0.37 | 0.9 (0.6-1.5) | 0.76 | 1.2 (1.0-1.4) | 0.13 | 1.2 (0.9-1.6) | 0.15 |
| Centre (frailty) | | 0.007 | | 0.03 | | 0.24 | | 0.01 |

Abbreviations: 10y, 10 years; CBT, cord blood transplant recipients; CR, complete remission; Haplo, MSD, HLA-matched sibling donor; MUD 10/10, 10/10 HLA-matched unrelated donor; sec AML, secondary AML; Tx, transplantation.

posttransplant Cy in our cohort was too low to assess its impact of GvL effects in that group of patients.

Importantly, OS and LFS were comparable with the 4 donor types, although there was a suggestion for lower OS with haplo than with MSD. Looking at causes of death, we observed a trend for higher infection-related mortality in haplo recipients than in patients given grafts from other donor types. Interestingly, in contrast to the results reported by the BMT-CTN network study comparing haplo ($n = 50$) and CBT ($n = 50$) following fludarabine + 2 Gy TBI where 1-year NRM was 24% with CBT and only 7% with haplo (19), we observe similar 2-year NRM in CBT (16%) and haplo (22%) patients. Reasons for these discrepancies are unclear but might be perhaps explained by different underlying diseases (only AML in the current study versus various diagnoses in the BMT-CTN study) or by strict inclusion criteria in the BMT-CTN study while current analyses report data from "real life" patients. There was also perhaps a center effect (T-cell-repleted haplo is rather a newer transplantation strategy in Europe) since center

(frailty) was significantly associated with NRM in multivariate analyses. Finally, another possible confounding factor is that, while almost all MSD and MUD patients were given PBSC, approximately half of the haplo patients received bone marrow as stem cell source. However, a recent study from our group comparing PBSC with BM in non-T-cell depleted haplo AML patients (given various conditioning regimen) observed similar outcomes with the two stem cell sources, with the exception of faster engraftment and higher incidence of GVHD in PBSC patients (46).

Our study revealed a high incidence of grade III-IV acute GVHD in CBT recipients (15%). A recent study from our group observed that the low incidence of acute GVHD associated with CBT is limited to CBT patients receiving ATG in the conditioning regimen (47). In concordance with this observation, the incidence of grade III-IV acute GVHD in our study was similar to what has been reported by the Seattle (18%; ref. 41) or the Minesotta (19%; ref. 48) teams that used a similar ATG-free nonmyeloablative HCT platform.

Table 3. Multivariate analyses for relapse, NRM, and GRFS (nonproportionality for donor type before and after day 100)

| | Relapse | | NRM | | GRFS | |
|----------------------------|---------------|--------|---------------|--------|---------------|--------|
| | HR (CI) | P | HR (CI) | P | HR (CI) | P |
| MSD (reference) | 1.0 | | 1.0 | | 1.0 | |
| MUD 10/10 within 100 days | 0.9 (0.7-1.2) | 0.55 | 2.3 (1.6-3.4) | <0.001 | 1.1 (0.8-1.6) | 0.50 |
| MUD 10/10 after 100 days | 0.9 (0.6-1.2) | 0.42 | 2.5 (1.7-3.7) | <0.001 | 1.3 (1.1-1.7) | 0.001 |
| Haplo within 100 days | 1.0 (0.6-1.6) | 0.95 | 2.4 (1.2-4.9) | 0.01 | 1.4 (0.8-2.3) | 0.21 |
| Haplo after 100 days | 1.2 (0.7-2.2) | 0.42 | 1.3 (0.5-3.5) | 0.63 | 0.7 (0.5-1.1) | 0.16 |
| CBT within 100 days | 1.1 (0.8-1.4) | 0.74 | 1.8 (1.1-2.9) | 0.02 | 1.6 (1.1-2.2) | 0.01 |
| CBT after 100 days | 1.3 (0.9-1.8) | 0.19 | 1.0 (0.5-1.8) | 0.89 | 0.6 (0.5-0.8) | 0.002 |
| CR2 vs. CR1 | 1.2 (1.0-1.5) | 0.1 | 0.9 (0.6-1.2) | 0.40 | 1.0 (0.8-1.2) | 0.95 |
| Age (per 10y) | 0.9 (0.9-1.0) | 0.08 | 1.4 (1.2-1.6) | <0.001 | 1.0 (0.9-1.1) | 0.61 |
| Year of Tx | 1.0 (1.0-1.0) | 0.88 | 1.0 (0.9-1.0) | 0.08 | 1.0 (1.0-1.0) | 0.047 |
| Good risk (reference) | 1.0 | | 1.0 | | 1.0 | |
| Intermediate risk | 1.5 (1.0-2.1) | 0.04 | 1.0 (0.7-1.7) | 0.84 | 1.4 (1.0-2.0) | 0.03 |
| Adverse | 3.4 (2.3-5.1) | <0.001 | 0.9 (0.5-1.6) | 0.80 | 2.1 (1.5-2.9) | <0.001 |
| Sec. AML | 1.0 (0.8-1.4) | 0.78 | 1.2 (0.8-1.8) | 0.26 | 1.0 (0.8-1.3) | 0.88 |
| Female D to male vs. other | 0.7 (0.6-0.9) | 0.02 | 1.7 (1.3-2.3) | <0.001 | 1.2 (1.0-1.5) | 0.03 |
| Patient CMV positive | 0.9 (0.7-1.1) | 0.22 | 1.1 (0.8-1.4) | 0.46 | 1.1 (0.9-1.3) | 0.28 |
| Donor CMV positive | 1.3 (1.1-1.5) | 0.01 | 1.0 (0.8-1.3) | 0.91 | 1.1 (1.0-1.3) | 0.10 |
| Centre (frailty) | | 0.11 | | <0.001 | | 0.27 |

Abbreviations: 10y, 10 years; CBT, cord blood transplant recipients; CR, complete remission; MSD, HLA-matched sibling donor; MUD 10/10, 10/10 HLA-matched unrelated donor; sec AML, secondary AML; Tx, transplantation.

Table 4. Multivariate analyses for LFS and OS

| | LFS | | OS | |
|----------------------------|---------------|--------|---------------|--------|
| | HR (CI) | P | HR (CI) | P |
| MSD (reference) | 1 | | 1 | |
| MUD 10/10 | 1.1 (0.9–1.5) | 0.35 | 1.2 (0.9–1.6) | 0.18 |
| Haplo | 1.3 (0.9–2.0) | 0.16 | 1.4 (0.9–2.2) | 0.09 |
| CBT | 1.2 (0.9–1.5) | 0.3 | 1.1 (0.8–1.5) | 0.39 |
| CR2 vs. CR1 | 1.2 (0.9–1.5) | 0.22 | 1.1 (0.8–1.5) | 0.45 |
| Age (per 10y) | 1 (0.9–1.1) | 0.51 | 1 (0.9–1.1) | 0.43 |
| Year of Tx | 1 (1.0–1.0) | 0.58 | 1 (0.9–1.0) | 0.89 |
| Good risk (reference) | 1 | | 1 | |
| Intermediate risk | 1.6 (1.0–2.4) | 0.04 | 1.9 (1.2–3.1) | 0.01 |
| Adverse risk | 2.9 (1.8–4.5) | <0.001 | 3.4 (2.0–5.7) | <0.001 |
| Sec. AML | 1.3 (1.0–1.7) | 0.06 | 1.4 (1.0–1.8) | 0.04 |
| Female D to male vs. other | 0.9 (0.7–1.1) | 0.37 | 1 (0.7–1.2) | 0.74 |
| Patient CMV positive | 1 (0.8–1.2) | 0.88 | 1.1 (0.9–1.3) | 0.48 |
| Donor CMV positive | 1.1 (0.9–1.4) | 0.16 | 1.1 (0.8–1.3) | 0.43 |
| Centre (frailty) | | 0.25 | | 0.18 |

Abbreviations: 10y, 10 years; CBT, cord blood transplant recipients; CR, complete remission; MSD, HLA-matched sibling donor; MUD 10/10, 10/10 HLA-matched unrelated donor; sec AML, secondary AML; Tx, transplantation.

GRFS is increasingly recognized as a major endpoint in allo-HCT (30). Interestingly, while the number of CBT performed in Europe for AML is declining, our study observed a better GRFS beyond day 100 in CBT recipients than in MSD. This was due to a relatively low incidence of relapse in CBT recipients in the context of very low incidence of chronic GVHD. Interestingly, as reported previously (26), GRFS was comparable in single or double CBT recipients (Supplementary Table S2). Similarly, haplo patients had also an encouraging GRFS (no statistically different than CBT) due to a low incidence of chronic GVHD. In contrast, MUD recipients had a relatively low GRFS due to a high incidence of both grade III–IV acute and chronic GVHD. Although GRFS is a new important endpoint in allo-HCT as it might better reflect health status and quality of life than LFS, it has also some limitation and should not be used alone for decision making. Indeed, chronic GVHD grading has remained somewhat observer dependent, and patients with severe chronic GVHD can achieve a good quality of life after GVHD resolution.

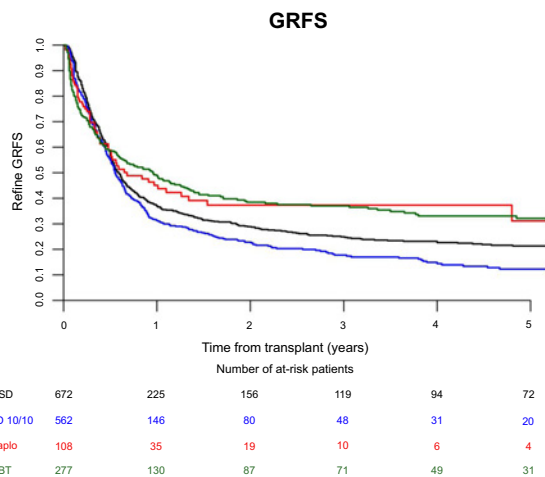
Main causes of death following this low-intensity conditioning regimen consisted of disease relapse, infections and

GVHD. Approaches to decrease the incidence of disease relapse might consist of increasing the intensity of the conditioning regimen (for example with the addition of treosulfan (49) or with radiolabeled antibodies (50, 51)) or adding disease-targeted therapies after transplantation (52, 53). Furthermore, recent studies have demonstrated that triple postgrafting immunosuppression with cyclosporine, MMF and sirolimus improved outcomes in MUD patients conditioned with fludarabine + 2 Gy TBI (54), while administration MMF at the dose of 3g/day (instead of 2 g/day) decreased the incidence of grade II–IV acute GVHD without affecting infection-related mortality of other transplantation outcomes in the double CBT setting (55).

There are some limitations in the study including missing data on comorbidity (56) other than Karnofsky score, minimal residual disease (57), and cytogenetic/molecular abnormalities in many patients. In addition, the very low number of MSD and MUD patients receiving posttransplant Cy as GVHD prophylaxis precluded us to add this potentially confounding factor in the multivariate Cox analyses. Another limitation inherent to registry study is that we do not have data on some pretransplant relevant events such as time to find the donor, additional cycles of chemotherapy, or early relapses that might have eliminated some of the more aggressive leukemia from the alternative donor transplant groups. Indeed, these latter were associated with a longer interval from diagnosis to transplantation (in CR1 patients) in comparison with MSD patients. However, this study is the largest one thus far comparing the impact of donor type in AML patients given grafts after fludarabine + 2 Gy TBI conditioning.

Conclusions

In this large cohort of AML patients transplanted in CR following low-dose TBI-based nonmyeloablative conditioning regimen, the relapse incidence was not affected by donor type suggesting that the intensity of GVL effects is comparable with these four transplant approaches. Furthermore, MUD patients had lower GRFS than MSD patients while CBT was associated with a better GRFS than MSD beyond day 100 suggesting that CBT remains a valid transplantation approach with this low-intensity conditioning regimen.

**Figure 2.**

GVHD relapse-free survival according to donor type.

List of institutions

The EBMT registry is a voluntary working group of more than 500 transplant centers, participants of which are required once a year to report all consecutive stem cell transplantations and follow-up. The list of institutions reporting data included in this study is provided in the Supplementary Data.

Disclosure of Potential Conflicts of Interest

D. Niederwieser reports receiving other commercial research support from Novartis. No potential conflicts of interest were disclosed by the other authors.

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Baron et al.

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